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Additional Prognostic Value of Coronary Flow Reserve in Diabetic and Nondiabetic Patients With Negative Dipyridamole Stress Echocardiography by Wall Motion Criteria

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Objectives The aim of this prospective, multicenter, observational study was to compare the prognostic value of Doppler echocardiographic-derived coronary flow reserve (CFR) in diabetic and nondiabetic patients with known or suspected coronary artery disease and negative dipyridamole stress echocardiography.

Background The prognostic value of CFR in diabetic patients with negative stress echocardiography remains unknown.

Methods The study group consisted of 1,130 patients (207 diabetics) with known ($n = 418$) or suspected ($n = 712$) coronary artery disease and negative stress echocardiography by wall motion criteria. All underwent dipyridamole (up to 0.84 mg/kg over 6 min) echocardiography with CFR evaluation of left anterior descending artery by Doppler. A value of CFR $\leq$2.0 was considered abnormal.

Results Coronary flow reserve was abnormal in 309 (27%) patients. During a median follow-up of 16 months, 98 events (8 deaths, 24 ST-segment elevation myocardial infarctions, and 66 non–ST-segment elevation myocardial infarctions) occurred. In addition, 101 patients underwent revascularization and were censored. Multivariable prognostic indicators were abnormal CFR ($p < 0.0001$), anti-ischemic therapy at the time of testing ($p = 0.002$), age ($p = 0.02$), and resting wall motion abnormality ($p = 0.05$). The event rate was markedly higher ($p < 0.0001$) for both diabetic and nondiabetic patients with abnormal CFR as compared with diabetic and nondiabetic patients with normal CFR. Of note, a preserved CFR off therapy identified diabetic and nondiabetic patients with better survival and comparable yearly event rates (2.2% vs. 2.0%, $p = 0.80$).

Conclusions Coronary flow reserve provides independent prognostic information in diabetic and nondiabetic patients with known or suspected coronary artery disease and negative dipyridamole stress echocardiography. In particular, a normal CFR off therapy is associated with better and similar survival in the 2 populations. (J Am Coll Cardiol 2007;50:1354–61) © 2007 by the American College of Cardiology Foundation

Risk stratification of diabetic patients is a major objective for the clinical cardiologist, given their increased risk for coronary artery disease (CAD) (1,2). Although stress echocardiography provides useful prognostic information in these patients (3–7), a negative test result is associated with less benign outcome in the presence of diabetes (7). This calls for more effective prognostic modalities in diabetic subjects.

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The combined evaluation of wall motion and coronary flow reserve (CFR) in the left anterior descending artery (LAD) during dipyridamole stress echocardiography has been recently proposed as a feasible (8) and accurate method for the diagnosis of CAD, increasing test sensitivity with modest loss in specificity (9–14). In a previous study, abnormal CFR was found to correlate with unfavorable outcome in patients with known or suspected CAD and negative stress echocardiography result by wall motion criteria (15). However, the relative prognostic importance of CFR over wall motion analysis remains to be established in the diabetic population. In fact, several studies, mainly in type 2 diabetes, have documented a reduced CFR even in the absence of coronary obstructive disease and using different techniques

(16). Coronary microcirculatory dysfunction affects the left ventricle globally (17) as well as regionally (16), and therefore the CFR assessment on LAD, which would be inadequate for CAD detection, is an excellent option for evaluating global coronary microcirculation conditions in these patients.

The aim of this prospective, multicenter, observational study was to compare the prognostic value of CFR in the LAD in diabetic and nondiabetic patients with known or suspected CAD and negative dipyridamole stress echocardiography for wall motion criteria.

Methods

Patients. The initial population comprised 1,544 patients prospectively enrolled at 5 Italian cardiology institutions (Lucca, Mestre, Cesena, Pisa, Napoli) from August 2003 to June 2006. All patients underwent stress echocardiography with CFR assessment of LAD by transthoracic Doppler ultrasound. Of the 1,544 patients initially selected for the study, 85 (6%) were excluded for inadequate echocardiographic image quality precluding satisfactory imaging of LAD flow, 31 (2%) for side effects requiring premature test interruption, and 298 (19%) for test positivity by wall motion criteria. Thus, 1,130 patients (629 men, age 63 ± 11 years) with a negative stress echocardiography by wall motion criteria formed the study group. Of them, 207 were diabetic patients (18). Indication to stress echocardiography was suspected CAD in 712 (63%) and risk stratification of known CAD (i.e., history of myocardial infarction, coronary revascularization, and/or angiographic evidence of >50% diameter coronary stenosis) in 418 (37%) subjects. Exclusion criteria were significant valvular or congenital heart disease, prognostically relevant noncardiac diseases (cancer, end-stage renal disease, or severe obstructive pulmonary disease), and inadequate acoustic window precluding satisfactory imaging of left ventricle (for 2-dimensional echocardiography) or of LAD flow Doppler (for CFR assessment). Arterial hypertension (19) and hypercholesterolemia (20) were defined according to standard definitions. According to individual needs and physicians' choices, 666 (59%) patients were evaluated after antianginal drugs had been discontinued, and 464 (41%) patients were evaluated during antianginal treatment (Table 1). Of the 207 diabetic patients, 159 were on oral antidiabetics, 46 on insulin therapy, and 2 on both. The study was approved by the institutional review board. All patients gave their written informed consent when they underwent stress echocardiography. When patients signed the written informed consent they also authorized physicians to use their clinical data. Stress echocardiography data were collected and analyzed by stress echocardiographers not involved in patient care.

Stress echocardiography. Transthoracic stress echocardiographic studies were performed with commercially available ultrasound machines (Sonos 5500-7500, Philips Ultrasound, Andover, Massachusetts; Sequoia C256, Acuson Siemens, Mountain View, California; and Vivid System 7, GE/Vingmed, Milwaukee, Wisconsin) equipped with multifrequency phased-array sector scan probe (S3–S8 or V3–V7) and with second harmonic technology. Two-dimensional echocardiography and 12-lead electrocardiographic monitoring were performed in combination with high-dose dipyridamole (up to 0.84 mg over 6 min) (21). Echocardiographic images were semiquantitatively assessed using a 17-segment, 4-point scale model of the left ventricle (22). A wall motion score index was derived by dividing the sum of individual segment scores by the number of interpretable segments. Ischemia was defined as stress-induced new and/or worsening of pre-existing wall motion abnormality. Rest wall motion abnormality was akinetic or dyskinetic myocardium with no thickening during stress. A test was normal in case of no rest and stress wall motion abnormality.

Coronary flow reserve was assessed during the standard stress echocardiography examination by an intermittent imaging of both wall motion and LAD flow (9). Coronary flow in the mid-distal portion of LAD was searched for in

Abbreviations and Acronyms

CAD = coronary artery disease

CFR = coronary flow reserve

LAD = left anterior descending coronary artery

NSTEMI = non–ST-segment elevation myocardial infarction

STEMI = ST-segment elevation myocardial infarction

Table 1 Characteristics of the Study Population

Age (yrs)	63 ± 11
Men	629 (56%)
Clinical history	
Prior myocardial infarction	310 (27%)
Prior coronary revascularization	321 (28%)
Prior CABG	61 (5%)
Prior PCI	260 (23%)
Known CAD	418 (37%)
Left bundle branch block	67 (6%)
Family history of CAD	231 (20%)
Diabetes	207 (18%)
Arterial hypertension	723 (64%)
Hypercholesterolemia	627 (55%)
Smoking habit	323 (29%)
Anti-ischemic therapy at the time of test	
Beta-blockers	335 (30%)
Calcium antagonists	224 (20%)
Nitrates	149 (13%)
At least 1 medication	464 (41%)
Echocardiogram	
Resting WMSI	1.14 ± 0.27
Resting LVEF (%)	56 ± 8
Resting WMA	341 (30%)
CFR	2.41 ± 0.58
CFR ≤2	309 (27%)

Data presented are mean ± standard deviation or number (%) of patients.

CABG = coronary artery bypass grafting; CAD = coronary artery disease; CFR = coronary flow reserve; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; WMA = wall motion abnormality; WMSI = wall motion score index.

the low parasternal long-axis section under the guidance of color Doppler flow mapping (23). In 402 (36%) patients with no visualization of color-coded blood flow from the LAD at the baseline condition, the procedure was attempted a second time during contrast enhancement with Sonovue (Bracco-Byk-Gulden, Konstanz, Germany) in bolus (0.5 ml intravenously) (Fig. 1).

All studies were digitally stored to simplify off-line reviewing and measurements. Coronary flow parameters were analyzed off-line by use of the built-in calculation package of the ultrasound unit. Flow velocities were measured at least twice for each study: at baseline and at peak stress (before aminophylline injection). At each time point, 3 optimal profiles of peak diastolic Doppler flow velocities were measured, and the results were averaged. Coronary flow reserve was defined as the ratio between hyperemic peak and basal peak diastolic coronary flow velocities. A value of CFR $\leq$2 was considered abnormal. All observers were trained by the same senior investigator (F.R.), who granted consistency in data acquisition, storage, and interpretation, also through intensive joint reading sessions. All investigators of contributing centers passed quality control criteria for regional wall motion and Doppler interpretation before entering the study as previously described (24). The previously assessed intra- and interobserver variability for measurements of Doppler recordings and regional wall motion analysis assessment were <10% (9).

Follow-up data. Outcome was determined from patients' interview at the outpatient clinic, hospital chart reviews, and telephone interviews with the patient, his/her close relative, or referring physician. The clinical events recorded during the follow-up were death, nonfatal acute coronary syndromes (ST-segment elevation myocardial infarction [STEMI] or non–ST-segment elevation myocardial infarction [NSTEMI]), and clinically driven coronary revascularization (surgery or angioplasty). In order to avoid misclassification of the cause of death (25), overall mortality was considered. ST-segment elevation myocardial infarction was defined by typical symptoms, ST-segment elevation on electrocardiogram, and cardiac enzyme changes. Non–ST-segment elevation was an acute coronary syndrome causing typical chest pain, cardiac enzyme elevation, and/or electrocardiographic modifications consistent with acute ischemia (26) requiring hospitalization. Follow-up data were analyzed for the prediction of death, STEMI, or NSTEMI.

Statistical analysis. Continuous variables are expressed as mean $\pm$ standard deviation. Differences in continuous variables were assessed with the unpaired *t* test; the chi-square test was used for categorical variables. Survival rates were estimated with Kaplan-Meier curves and compared by the log-rank test. Patients undergoing coronary revascularization were censored at the time of the procedure. Only the first event was taken into account. Annual event rates were obtained from Kaplan-Meier estimates to take censoring of the data into account. The association of selected variables with outcome was assessed with the Cox proportional hazard model using univariate and stepwise multivariate procedures. A significance of 0.05 was required for a variable to be included into the multivariate model, whereas 0.1 was the cutoff value for exclusion. Hazard ratios with the corresponding 95% confidence intervals were estimated. Statistical significance was set at a value of $p < 0.05$. Statistical Package for the Social Sciences (SPSS release 13.0, SPSS Inc., Chicago, Illinois) was used for analysis.

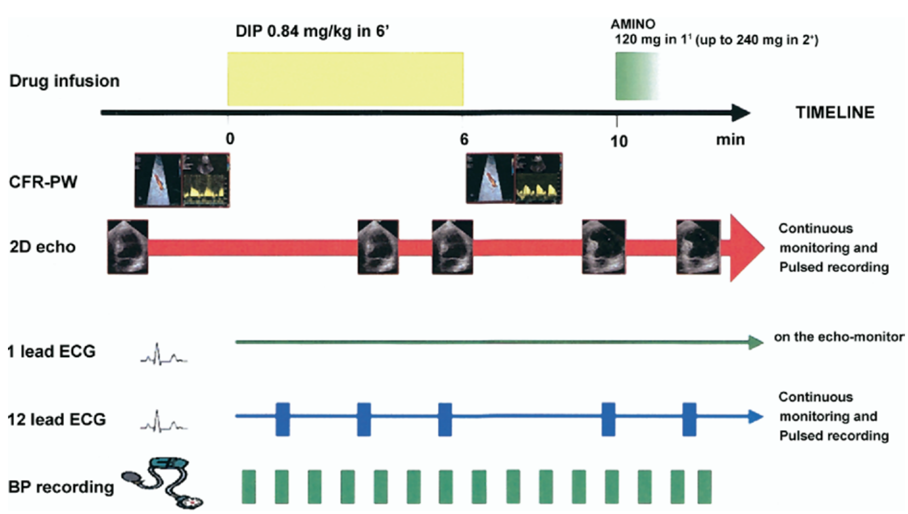

Figure 1 **Protocol of Dipyridamole Stress Echocardiography**

The stress protocol was based on the intermittent evaluation of wall motion and coronary flow reserve (CFR) in the left anterior descending artery during dipyridamole (DIP) infusion. BP = blood pressure; PW = pulsed wave; 2D echo = 2-dimensional echocardiography.

Results

Stress echocardiography. No major complications occurred during the test. Of 1,130 patients, 341 (30%) exhibited resting wall motion abnormality (165 on the LAD territory), and 789 (70%) no wall motion abnormality at rest. Coronary flow reserve was abnormal in 309 (27%) cases. No difference in CFR was observed between the 165 patients with resting wall motion abnormality on the LAD territory and those with normal regional function (2.34 ± 0.66 vs. 2.42 ± 0.57, p = 0.13). Patients with abnormal CFR were older (65 ± 11 years vs. 63 ± 11 years, p = 0.003), had higher incidence of hypercholesterolemia (64% vs. 52%, p = 0.0004), and arterial hypertension (69% vs. 62%, p = 0.03), higher resting wall motion score index (1.19 ± 0.34 vs. 1.12 ± 0.25, p < 0.0001), and underwent stress echocardiography more frequently under anti-ischemic therapy (50% vs. 37%, p < 0.0001) than patients with normal CFR. No difference in resting flow diastolic velocity was found between hypertensives and normotensives (30 ± 10 cm/s vs. 30 ± 8 cm/s, p = 0.63), patients with and without hypercholesterolemia (30 ± 10 cm/s vs. 29 ± 8 cm/s, p = 0.34), and patients with and without resting wall motion abnormality (30 ± 10 cm/s vs. 29 ± 9 cm/s, p = 0.29). Patients with abnormal CFR had slightly higher resting flow velocities than patients with normal CFR (33 ± 11 cm/s vs. 29 ± 8 cm/s, p = 0.03) and markedly lower peak flow velocities (59 ± 19 cm/s vs. 74 ± 21 cm/s, p = 0.002).

In the 207 diabetic patients, the mean value of glycosylated hemoglobin (HbA_{1c}) was 6.9 ± 1.5%. Glycosylated hemoglobin was similar in diabetic patients with normal and abnormal CFR (7.0 ± 1.5% vs. 6.7 ± 1.5%, p = 0.82). Clinical and echocardiographic characteristics of the study population are reported in Table 1.

Follow-up events. During a median follow-up of 16 months (first quartile 8, third quartile 26 months), there were 98 hard events (8 deaths, 24 STEMI, and 66 NSTEMI). Twenty-seven events occurred in diabetic and 71 in nondiabetic patients (13% vs. 7.7%, p = 0.01). Patients on beta-blocking agents at time of testing had a higher incidence of events when compared with those off beta-blocking therapy (14% vs. 6.4%, p = 0.001). Additionally, 101 patients underwent revascularization (18 surgery and 83 angioplasty) after a median of 193 days from the index stress echocardiography: 29 diabetic and 72 nondiabetic patients (14% vs. 7.8%, p = 0.005). There were 59 revascularizations in patients with abnormal CFR and 42 in those with normal CFR (19% vs. 5%, p < 0.0001). The 3-year event rate associated with abnormal and normal CFR was not different (p = NS) between patients with or without resting wall motion abnormalities (38% vs. 36% and 11% vs. 9%, respectively).

Outcome prediction. Univariate and multivariate prognostic indicators are reported in Table 2. Abnormal CFR was the strongest independent predictor of future events (p < 0.0001), followed by anti-ischemic therapy at the time of testing (p = 0.002), age (p = 0.02), and rest wall motion abnormality pattern (p = 0.05) (Table 2).

Abnormal CFR was associated with markedly higher event rates (p < 0.0001) than normal CFR in both the diabetic and nondiabetic populations (Fig. 2).

The annual event rate in the entire population of diabetic and nondiabetic patients was 9.3% and 5.1%, respectively. When test negativity was obtained off therapy, the presence of a normal CFR identified a group of diabetic and nondiabetic patients with similar low annual event rate (2.2% vs. 2.0%, p = 0.80). Conversely, when CFR was abnormal, it was associated with higher risk in diabetic patients, independent of the presence of concomitant therapy.

Table 2 Univariate and Multivariate Prognostic Predictors

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age (yrs)	1.02 (1.00–1.04)	0.009	1.02 (1.00–1.04)	0.02
Gender (male)	0.81 (0.54–1.20)	0.30		
Prior infarction	1.31 (0.86–1.98)	0.21		
Prior revascularization	0.67 (0.42–1.08)	0.10		
Known CAD	1.18 (0.89–1.76)	0.42		
Left bundle branch block	1.18 (0.52–2.70)	0.69		
Family history of CAD	1.14 (0.68–1.90)	0.63		
Diabetes	1.85 (1.19–2.89)	0.006		
Hypertension	1.49 (0.96–2.31)	0.08		
Hypercholesterolemia	1.51 (0.99–2.31)	0.06		
Smoking habit	0.96 (0.61–1.51)	0.86		
Anti-ischemic therapy	2.39 (1.59–3.60)	<0.0001	1.96 (1.29–2.98)	0.002
CFR ≤2	5.43 (3.60–8.19)	<0.0001	4.95 (3.26–7.50)	<0.0001
Left ventricular ejection fraction	0.99 (0.97–1.01)	0.18		
Resting WMSI	1.63 (0.89–2.99)	0.11		
Resting WMA	1.64 (1.10–2.45)	0.02	1.50 (1.00–2.25)	0.05

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

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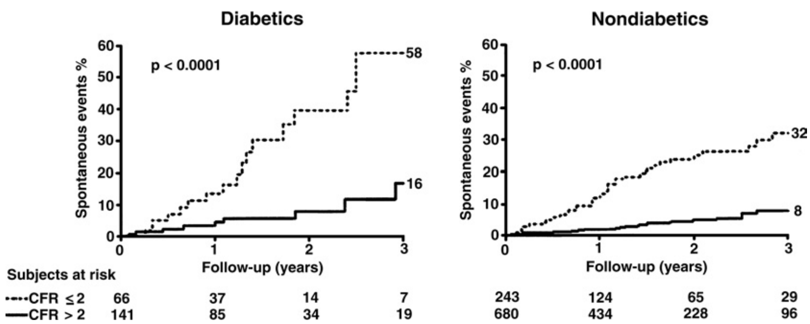

Figure 2 **Kaplan-Meier Survival Curves**

Event rate for diabetic and nondiabetic patients with coronary flow reserve (CFR) >2 or ≤2.

Discussion

Stress echocardiography is a recognized technique for the prognostic assessment of diabetic patients (3–7). In one study, the result of test similarly identified groups with different risk profile in diabetic and nondiabetic subjects (7). Nevertheless, a negative test was less prognostically benign in diabetic patients than in age-matched nondiabetic patients (7), consistent with the increased cardiovascular risk associated with diabetes (1,2,7,27–29). The search for more accurate and effective risk stratification strategies is critical in diabetic patients in order to optimize therapeutic interventions. In the current study, we found abnormal CFR in the LAD to be a strong, independent and additive prognostic indicator in a large cohort of patients with known or suspected CAD and negative dipyridamole stress echocardiography by standard wall motion criteria. Clinically driven revascularizations were also more frequent in patients with reduced than in those with preserved CFR. In keeping with previous findings (30), concomitant anti-ischemic therapy was also a strong predictor of unfavorable outcome. Interestingly, the interaction between CFR and anti-ischemic therapy provided an effective prognostic stratification. In the context of a relatively low-risk clinical setting, as that of patients with negative stress echocardiography result (7) off therapy, a preserved CFR identified diabetic and nondiabetic patients with better survival and comparable yearly event rate. On the basis of present results, a negative test off therapy with normal CFR confers a benign prognosis independent of diabetes. Conversely, abnormal CFR was associated with markedly increased annual risk in diabetic patients that was only marginally modulated by concomitant therapy. It is in this subset of patients that a more aggressive approach is warranted with a tight metabolic control, maximal anti-ischemic therapy, and a more frequent follow-up by noninvasive stress testing. A watchful surveillance is strongly recommended in those with a test negativity under medical therapy and abnormal CFR. Consistent with previous reports (31), no relation between HbA_{1c} and CFR was found in our study population. Explanations for reduced CFR in the absence of stress-induced wall motion abnormalities include mild-to-moderate epicardial coronary artery stenosis (32), severe epicardial coronary artery stenosis in presence of anti-ischemic therapy (33–36), and severe microvascular coronary disease in presence of patent epicardial coronary arteries (37,38). Noteworthy, an impairment of CFR has been documented in both type 1 and 2 diabetes mellitus without coronary artery stenosis by using different techniques (39–41). All these pathophysiological conditions may determine impairment of CFR and may adversely affect prognosis (15,27,41–45) (Fig. 3). Contrast ultrasound studies have demonstrated that myocardial perfusion abnormalities of clear prognostic impact can occur even when wall motion response is normal (46). Also, studies have shown that when there is existing wall motion abnormality at rest, the lack of biphasic response or worsening of wall motion has a very poor ability to exclude CAD (47). The unchanged wall motion response can still coexist with residual CFR, possibly mostly in the subepicardial layer, which is not reflected in changes in wall motion during stress but may exert prognostically beneficial antiremodelling and antiarrhythmic effects (48). In fact, the regional wall motion response during stress is tightly linked to subendocardial—rather than transmural or subepicardial—perfusion (49).

In recent years, vasodilator stress echocardiography with combined assessment of CFR in the LAD has entered the echocardiography lab as a feasible technique (8), providing additional diagnostic value over conventional wall motion analysis (9–14). However, the relative prognostic effect of CFR remains largely unexplored. In a previous study, abnormal CFR was independently associated with the occurrence of spontaneous events or late revascularizations in unselected patients with unchanged wall motion contractility during stress (15). In addition, abnormal CFR was a strong predictor of death or worsening of clinical status in nonischemic dilated cardiomyopathy (50). Finally, CFR was predictive of ventricular remodeling—a recognized indicator of unfavorable outcome (51)—after acute myocardial infarction treated by primary angioplasty (52).

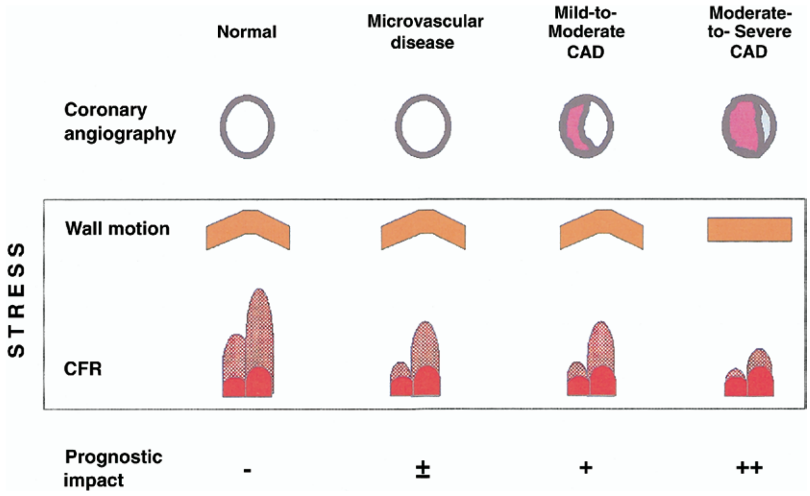

Figure 3 **Synthetic View of Different Coronary Anatomic and Prognostic CFR Conditions**

A synthetic view of the different coronary anatomic **(first row)** and prognostic coronary flow reserve (CFR) conditions **(last row)** underlying wall motion and CFR response during stress **(framed)**. In normal conditions **(left)**, there is normal coronary anatomy **(upper row)**, normal wall motion response **(second row)**, and normal CFR response **(third row)**, with 3-fold increase in peak diastolic flow velocity during stress **(dotted)** versus baseline **(full profile)**. An abnormal CFR with normal wall motion response can be found in presence of prognostically meaningful microvascular disease **(second column from left)** or mild-to-moderate epicardial stenosis **(third column from left)**. With more advanced epicardial coronary artery stenosis **(far right column)**, the reduction of CFR is consistently associated with wall motion abnormalities of obvious unfavorable prognostic impact (− = good prognosis; ± = possibly unfavorable prognosis; + = unfavorable prognosis; ++ = very unfavorable prognosis). CAD = coronary artery disease. Redrawn and modified from Picano et al. (32).

In this study, there was no central reading. Stress echocardiography and CFR measurement were interpreted in the peripheral centers and entered directly in the data bank. This system allowed substantial sparing of human and technologic resources, but it was also the logical prerequisite for a large scale study, designed to represent the realistic performance of the test rather than the results of a single lab—or even a single person—working in a highly dedicated echocardiography laboratory. Because the assessment of the echocardiograms was qualitative and subjective, variability in reading the echocardiograms might have modulated the results of individual centers (45). However, all our readers in individual centers had a long-lasting experience in echocardiography, passed the quality control in stress echocardiography reading as previously described (53), and had extensive experience on performance and interpretation of CFR also through joint reading sessions. One limitation of the Doppler technique is related to the need of a maximal vasodilation in order to compare rest and peak diastolic velocities, whereas the rest velocities may exert a prognostically significant meaning only when measured in a quantitative way as it happens with positron emission tomography (54). The study was not designed to address the effect of antidiabetic therapy; therefore enrolling centers evaluated each single patient according to referring physicians' prescriptions. We cannot also exclude that during the follow-up period antidiabetic therapy may have been changed in relation to glycemic and HbA_{1c} levels improving the overall metabolic state.

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